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NF2

1996 — 1997

Molecular Biology & Genetics

- Gene for NF2 localized to 22q12 (formal separation of NF1 and NF2) 1987
- • *NF2* gene cloned 1993
  • *NF2* gene product identified as Merlin/ Schwannomin 1993
- Mutation Rate for NF2 is ~6.5 x 10^{-6} 1993
- Two major isoforms (splice variants) of *NF2* identified 1994
- Correlations made between genotype and phenotype:
  •Parry et al.
  •Ruttledge et al.
  •Kluewe et al. 1996
- NF2 gene product shares similarity with the 4.1 family of cytoskeleton-associated proteins – Specifically the ERM proteins 1997

Cellular Biology

- Merlin is expressed in the nervous system, smooth muscle, Schwann cells, melanocytes, RBCs, endothelial cells, and neurons such as Purkinje cells and motor neurons, but not in glial cells 1996
- Immunocytochemistry shows Merlin localized to the cell membrane (filopodia, ruffling membrane, and leading edge) 1996
- Truncated forms of Merlin are not detected in NF2 tumors, suggesting protein instability and degradation 1997
- Merlin self-interaction (N- to C-terminal) is involved in growth suppression 1997
- Merlin co-localized with CD44 and the actin cytoskeleton 1997

Pathobiology

- NF2 mutations detected in ~50%-80% of NF2 tumors 1992+
- Merlin (NF2 mutation) is implicated in breast cancers and colorectal cancers 1994
- Merlin is lost in ~60% of sporadic meningiomas and ~80% of sporadic schwannomas 1994
- Merlin (NF2 mutation) is implicated in mesotheliomas 1995
- Germline mutations in NF2 found in at least two-thirds of all individuals with typical bilateral vestibular schwannoma 1996

Technology/ Animal Models

- Drosophila NF2 mutations isolated and characterized 1997
- Drosophila homologue of NF2 (Merlin) identified 1997
- Inactivation of mouse NF2 gene results in embryonic lethality between day 6.5 and 7.0 1997
- NF2 heterozygous (+/-) mice are developed; predisposed to cancer at advanced age, but don't develop the hallmark tumors of NF2 1997

Imaging, Detection & Diagnosis

- Type 2 neurofibromatosis first described by Dr. Wishart 1820
- Type 1 neurofibromatosis1st identified in the literature by Dr. Friedrich von Recklinghausen 1882
- NF2 characterized by schwannomas of the 8th cranial nerve – can also involve schwannomas of other cranial nerves, meningiomas, ependymomas, and ocular manifestations 1987
- Gadolinium-enhanced MRI made available for imaging, detection and diagnosis of vestibular schwannoma – lesions as small as 2 mm are detectable 1988
- Diagnostic criteria for NF2 outlined:
  •Bilateral masses of the 8th cranial nerve; or
  •1 or more 1st degree relative with NF2 + unilateral vestibular mass of 8th cranial nerve; or
  •2 of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities 1990
- Two types of NF2 identified:
  (1) Gardner type – mild with late onset and few tumors other than vestibular schwannoma
  (2) Wishart type – severe, early onset with multiple tumors 1992
- Mosaicism at NF2 locus is uncommon and probably under-recognized; unilateral vestibular schwannoma, ipsilateral intracranial tumors, schwannomatosis, and/or asymmetric involvement 1996
- Schwannomatosis described as a separate clinical entity from other forms of NF: multiple schwannomas without evidence of vestibular schwannoma 1996
- Diagnostic criteria for NF2 outlined:
  •Bilateral vestibular schwannoma; or
  •1 or more 1st degree relative with NF2 + unilateral vestibular schwannoma at <30 years; or
  •2 of the following: meningioma, glioma, schwannoma, juvenile posterior lenticular opacities 1997

Epidemiology

- Birth incidence of NF2 is determined to be ~1:33,000-40,000 1992
- Diagnostic prevalence of NF2 is ~1:200,000 because of late onset and early death 1992
- Correlations made between genotype and phenotype:
  •Nonsense/frameshift mutations = severe phenotypes
  •Splice-site mutations = variable phenotype within/ between families
  •Very few non-truncating mutations detected
  •Mutations not detected by exon-scanning = mild phenotype 1996

Experimental Therapeutics

- First auditory brainstem implant for treatment of hearing loss from NF2 1979
- FDA granted an Investigational Clinical Trial of a multichannel Auditory Brainstem Implant for NF2 1994
- Calpain inhibitors or calcium channel-blocking agents could prevent growth/relapse of tumors (in vitro) – more studies required 1995
- Aminoglycosides suppress expression of nonsense mutations of NF2 and modify the neoplastic phenotype of tumor cells in culture 1996
- SU-101 tested in Phase II trial for patients with recurrent malignant gliomas 1997

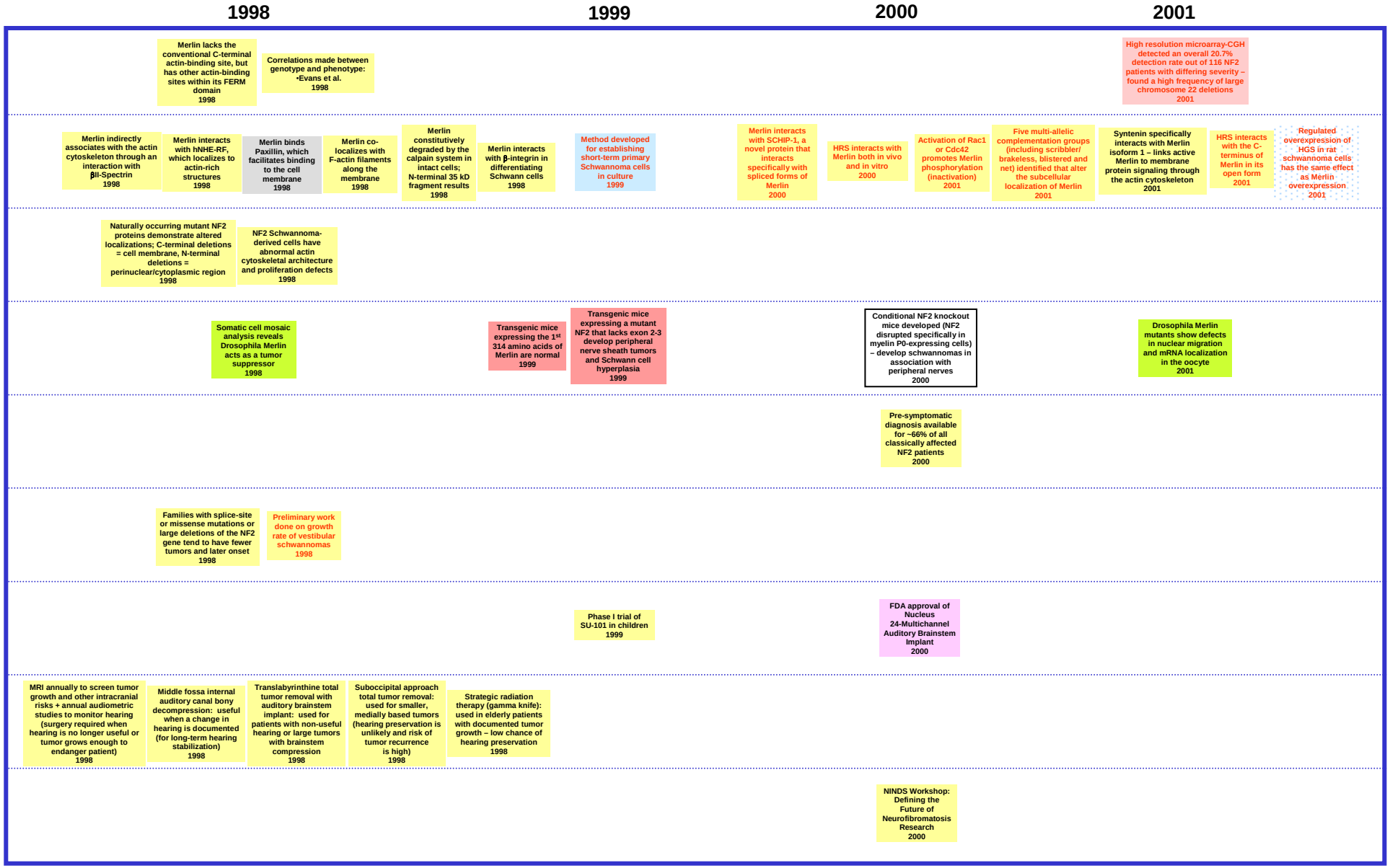
Symptom Management

- Recommended screening:
  •Routine eye exams
  •Enhanced MRI scanning should occur annually, beginning in the teens
  •Surveillance of at-risk but asymptomatic individuals 1980s
- Total excision of vestibular schwannomas or radiation therapy 1991
- Stereotactic radiosurgery (gamma-knife) available for vestibular schwannoma (typically results in loss of hearing) 1992
- Hearing preservation/ augmentation strategies: hearing aids, cochlear implants, training in lip reading and/or sign language 1992
- Partial excision of vestibular schwannoma in cases of large tumors 1993

Important Meetings & Symposia

- Foundation of NNFF 1978
- NIH Consensus Development Conference on Neurofibromatosis: delineated NF1 from NF2 and diagnostic criteria for each 1987
- Foundation of NF, Inc. 1988
- NIH Consensus Development Conference on Acoustic Neuroma 1991
- DoD Neurofibromatosis Research Program (NFRP) established 1996
- NNFF Clinical Care Advisory Board: Diagnostic Evaluation and Management of NF1 and NF2 1997
- House Ear Institute & NNFF workshop on NF2: reviewed current knowledge, made short-term and long-term goals 1997

Neurofibromatosis Type 2 (NF2)



NF2

Linked research
Abc NFRP-funded research